Complete Summary

GUIDELINE TITLE

The role of colony-stimulating factor (CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer.

BIBLIOGRAPHIC SOURCE(S)

Campbell C, Bramwell V, Charette M, Oliver T. Role of colony-stimulating factor in patients receiving myelosuppressive chemotherapy for treatment of cancer. Curr Oncol 2003;10(2):102-26.

Systemic Treatment Disease Site Group. Campbell C, Bramwell V, Charette M, Oliver T. The role of colony-stimulating factor (CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Dec [online update]. 33 p. (Practice guideline report; no. 12-2). [76 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Cancer
- Myelosuppression

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Prevention
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate if granulocyte and granulocyte macrophage colony-stimulating factor (G-CSF and GM-CSF, jointly referred to as CSF) are effective in the management of adult cancer patients with solid tumours (including lymphomas) who are receiving myelosuppressive chemotherapy
- Specifically, to evaluate if: (1) CSF allows maintenance of chemotherapy dose, reduces important adverse clinical outcomes, and results in improved survival, (2) CSF allows dose intensification of chemotherapy and results in improved survival, (3) CSF during established episodes of febrile neutropenia improves outcomes such as survival, duration of fever, and days of hospitalization or on antibiotics and thus indirectly affects quality of life (QOL), (4) the CSFs currently available for clinical use differ in their efficacies and toxicities, (5) the clinically available CSFs have differing doses and schedules that not only maintain efficacy but also have benefits in terms of convenience or cost, and (6) CSF influences the occurrence or resolution of chemotherapy-induced mucositis

TARGET POPULATION

Adult cancer patients with solid tumors receiving myelosuppressive chemotherapy

Note: With the exception of lymphoma, hematologic malignancies are excluded.

INTERVENTIONS AND PRACTICES CONSIDERED

Use of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF)

MAJOR OUTCOMES CONSIDERED

- Events that might affect quality of life and/or resource utilization (febrile neutropenia, antibiotic usage, duration of hospitalization, toxicity, quality of life measurements)
- Indicators of improved efficacy of chemotherapy related to CSF use (response rates, progression-free and overall survival).

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature was searched using the MEDLINE (Ovid) (1966 through September 2002), CANCERLIT (Ovid) (1983 through July 2002), and Cochrane Library (Issue 3, 2002) databases. In addition, the Physician Data Query clinical trials database and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1995-2002), the European Society for Medical Oncology (1998, 2000), and the American Society of Hematology (1997-2002) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for relevant clinical practice guidelines. In addition, recommendations on the use of granulocyte colony-stimulating factor (G-CSF) from the American Society of Clinical Oncology and the Ontario Drug Benefits Program were reviewed. Reference lists from relevant articles and reviews were searched for additional trials.

The literature search combined disease specific terms (neoplasms/ or cancer:.tw. or malignan:.tw. or tumour:.tw.) with treatment specific terms (granulocyte colony-stimulating factor/ or granulocyte colony-stimulating factor.mp. or granulocyte macrophage colony-stimulating factor/ or granulocyte macrophage colony-stimulating factor.mp. or colony-stimulating factors/ or hematopoietic cell growth factors/ or haemopoietic growth factors.mp. or g-csf.tw. or gcsf.tw. or gm-csf.tw. or gmcsf.tw. or filgrastim.tw. or neupogen.tw. or leukine.tw. or sargramostim.tw. or molgramostim.tw. or leucomax.tw. or lenograstim.tw.) with search specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, and economic evaluations.

Inclusion Criteria

Articles were selected for inclusion if they were randomized trials of CSF in adult cancer patients with solid tumours (including lymphomas) receiving myelosuppressive chemotherapy evaluating:

- the same starting doses of chemotherapy in each arm, comparing CSF to control/placebo
- the planned dose intensification of chemotherapy supported by CSF
- the value of CSF in promoting recovery from febrile neutropenia
- different types of colony-stimulating factors
- different doses or schedules of CSF
- the occurrence and/or resolution of chemotherapy-related mucositis with CSF

Abstract data were excluded from the first and second items in this list because of the number of full-text reports available but were considered for all other sections.

Practice guidelines, meta-analyses, or systematic reviews were eligible for inclusion if they were explicitly based on randomized trials related to one or more of the guideline questions.

Outcomes of interest were events that might affect quality of life and/or resource utilization (febrile neutropenia, antibiotic usage, duration of hospitalization,

toxicity, quality of life measurements) and indicators of improved efficacy of chemotherapy related to CSF use (response rates, progression-free and overall survival).

Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they:

- were letters, editorials, or phase I or phase II non-randomized trials
- included patients with non-lymphoma hematological malignancies $\geq$50% of the patient population
- evaluated CSF with high-dose chemotherapy and autologous bone marrow or peripheral blood stem cell transplantation
- evaluated CSF with concurrent chemoradiotherapy
- evaluated CSF with dual receptor activity (e.g., IL-3 and G-CSF)

NUMBER OF SOURCE DOCUMENTS

A total of 63 randomized trials and two clinical practice guidelines were identified in the literature search and deemed eligible for review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

To address the first question (see "Guideline Objectives" field), results were pooled to determine the effect of colony-stimulating factor (CSF) on febrile neutropenic events across 16 trials of standard chemotherapy. A sensitivity analysis was performed to restrict the analysis to studies involving only granulocyte colony-stimulating factor (G-CSF). The numbers of events of febrile neutropenia were combined using the meta-analytic software program RevMan 4.1 (Metaview © Update Software). The random effects model was chosen as the more conservative estimate of effect. Results are expressed as the relative risk (RR) of an event in the CSF group compared with the control group with a 95% confidence interval. The significance tests are two-tailed. For the other outcomes of interest in this section, response and survival, the Systemic Treatment Disease Site Group (DSG) determined that the clinical heterogeneity was too great to pool data across trials.

In addressing questions two to five, it was judged inappropriate by the Systemic Treatment Disease Site Group to pool response and survival data, as the trials dealt with many different malignancies, chemotherapy regimens, and CFS dose/schedules.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

For Section 1, the results of the meta-analysis confirm the benefits of colony-stimulating factor (CSF) in reducing the incidence of febrile neutropenia. For this section, the Systemic Treatment Disease Site Group (DSG) also discussed the use of CSF to maintain standard doses of chemotherapy drug regimens where patients are not tolerating them because of neutropenia. This clinical situation is not well informed by the evidence. The argument to use CSF to maintain standard drug doses is indirect and comes from randomized trials in which clinical outcomes have been poorer in patients randomized to receive lower than standard doses compared with conventional doses of chemotherapy. Moreover, there are no trials indicating that the use of CSF to maintain doses in patients who are intolerant actually improves outcome. An alternative hypothesis is that those who do not tolerate standard doses may be the ones who are destined to have a poorer outcome anyway, perhaps because of a larger disease burden. There is no evidence to address this hypothesis either.

Guidelines from the American Society of Clinical Oncology (ASCO) and from the Ontario Drug Benefit (ODB) recommend the use of granulocyte colony-stimulating factor (G-CSF) to maintain drug doses in patients with potentially curable tumours who do not tolerate standard-dose chemotherapy because of neutropenia. Potentially curable patients are defined in the Ontario Drug Benefit guideline as those patients with testicular cancer, Hodgkin´s disease, and pediatric cancers. However, the available evidence does not support this restrictive interpretation. With these caveats, this practice guideline accepts the recommendations of other evidence-based guidelines in the spirit that 1) lack of high quality evidence is an insufficient basis to overturn either a conventional practice or one recommended by another credible guideline, and 2) the hypothesis governing this practice is a reasonable one in light of indirect evidence. However, we support trials that would address the issue specifically.

For Section 2, the available data on the effects of chemotherapy dose intensification supported by CSF on survival showed significantly positive results in four out of fourteen trials. However, a comparison arm of one of the trials also detected a survival benefit for dose intensification without CSF. On this basis, the Systemic Treatment DSG felt that the use of CSF to support the delivery of dose-intensified chemotherapy remained experimental.

For Section 3, the available data showed that the use of CSF in established febrile neutropenia produced statistically significant but clinically modest improvements in several measures of recovery from febrile neutropenia. As many patients with febrile neutropenia make a rapid and uncomplicated recovery on intravenous

antibiotics, it is unlikely to be cost-effective to use CSF in all cases. Patients not defervescing within 48 hours of starting antibiotics, who remain neutropenic, are at more risk for a complicated and prolonged recovery, and thus might benefit from CSF therapy. However, none of the available trials address this situation. Similarly, as recommended in the guideline produced by the American Society of Clinical Oncology, it may also be most reasonable to reserve CSF use for patients with factors predictive of a poor outcome (e.g., profound neutropenia [absolute neutrophil count <100/microliters] pneumonia, hypotension, multi-organ dysfunction, or invasive fungal infection). Thus, the Systemic Treatment DSG felt that immediate CSF may be a reasonable option for some patients with febrile neutropenia, but this would depend on the clinical circumstances.

For Section 4, direct comparisons suggested G-CSF and granulocyte macrophage colony-stimulating factor (GM-CSF) had similar efficacy and did not demonstrate significant differences in side effects. Globally, across all sections of this guideline, the reported incidences of side effects seemed greater in trials using GM-CSF, in contrast with G-CSF, but this comparison is subject to bias. Thus, the Systemic Treatment DSG did not feel it could recommend the use of one specific product.

For Section 5, the available trials evaluated several different approaches to the dose/schedule of CSF. In studies of abbreviated schedules, although neutropenia was more common with short durations of CSF, this did not lead to increased incidences of the clinically most important outcome (i.e., febrile neutropenia). The Systemic Treatment DSG felt that some regimens showed promise, but further study was needed.

For Section 6, there was preliminary evidence from one trial that CSF would help prevent or treat mucositis. However the Systemic Treatment DSG felt there were insufficient data on which to make a recommendation for its use in these settings.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A number of economic analyses of the use of colony-stimulating factor (CSF) have been published. As none of these studies were performed in Canada, their relevance to the Canadian health care system is limited. Two studies have suggested that primary prophylaxis with CSF is justified when the anticipated risk of febrile neutropenia is greater than 25- to 40%, which is not the case with the majority of standard chemotherapy regimens for solid tumours. Further research is needed to determine the impact of CSF on Canadian health care resources. This should include an assessment of the threshold at which it is cost-effective to utilize CSF relative to the baseline risk of hospitalization for specific malignant neoplasms and according to various chemotherapy regimens. However, ultimately, it would be the responsibility of policy makers in the provincial jurisdiction to define economic questions relevant to the Canadian health care system.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 138 medical oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Systemic Treatment Disease Site Group (DSG) reviewed the results of the survey.

The Practice Guideline Report was circulated to 13 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eleven members of the PGCC returned ballots. Ten PGCC members approved the practice guideline report as written. Of the ten members, two members approved the practice guideline conditional on changes that are described in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

1. In the setting of standard-dose chemotherapy for solid tumours, the risk of neutropenic fever is insufficient to justify routine use of colony stimulating factor (CSF, which includes both granulocyte and granulocyte macrophage colony-stimulating factors) as primary prophylaxis. If a patient experiences an episode of febrile neutropenia or prolonged neutropenia, dose reductions and/or delays of chemotherapy remain the standard initial approach. It is reasonable to use CSF to avoid multiple dose reductions or delays in circumstances where randomized controlled trials have shown improved survival with maintenance of dose intensity.
2. The use of CSF to support the delivery of dose-intensified chemotherapy regimens can only be recommended in the context of randomized controlled trials evaluating regimens that seek to improve progression-free, disease-free, and/or overall survival.
3. Although data are limited, it is reasonable to use CSF to decrease duration of fever, antibiotic use, or hospitalization in patients with febrile neutropenia. Further studies are warranted to establish specific recommendations in this situation.
4. It is not possible to make firm recommendations for a specific type of CSF. More data are available for granulocyte colony-stimulating factor (G-CSF), but further comparative studies of both agents are warranted.
5. There are insufficient data to support specific recommendations for dose/schedules of CSF that differ from those currently recommended by the manufacturer. However, some schedules in which CSF is delayed or abbreviated are promising and could be cost-effective. Therefore, this issue deserves further study.
6. There is preliminary evidence that CSF helps prevent or treat mucositis. However, the Systemic Treatment Disease Site Group felt there were

insufficient data on which to make a recommendation for its use in these settings.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials and clinical practice guidelines.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Trials of colony-stimulating factor (CSF) in which the same starting dose of chemotherapy was used in each treatment arm

  A meta-analysis of data from 16 trials showed that CSF reduced the risk of febrile neutropenia by 26% (Risk Ratio 0.74; 95% Confidence Interval, 0.63 to 0.87; p=0.0002). With respect to outcomes related to quality of life, CSF use was associated with a significant reduction in antibiotic usage and duration of hospitalization in two trials and had no effect in the other eight in which it was measured. Twelve trials reported no difference in overall median survival, while two small trials detected a significant increase related to CSF. However, further research is necessary to confirm these results. Dose intensity was significantly improved with CSF in four trials but without a corresponding improvement in response or survival rates.

- Trials evaluating planned dose intensification of chemotherapy supported by CSF

  Dose intensification of chemotherapy with CSF support did not achieve statistically significant differences in overall response rates in any trial. Four trials reported significant increases in progression-free survival with dose intensification of chemotherapy. Three trials reported a significant survival advantage for dose-intensive chemotherapy, while another trial reported a significant survival disadvantage.

- Trials evaluating the value of CSF in promoting recovery from febrile neutropenia

  Of six randomized trials that reported data, CSF was significantly associated with a shorter duration of febrile neutropenia in 1 trial, a shorter duration of hospitalization in 3 trials, a shorter duration of grade 4 neutropenia in 3 trials, and a shorter duration of antibiotic usage in 2 trials.

- Trials comparing different formulations of CSF

  Data from two studies showed significantly faster neutrophil recovery for granulocyte colony-stimulating factor (G-CSF) versus granulocyte macrophage colony-stimulating factor (GM-CSF), but the mean differences were small (0.5-1.5 days). There were no statistically significant differences between the two CSFs for any other measured clinical outcome.

- Trials evaluating dose/schedule of G-CSF or GM-CSF

  Studies looking at dosing schedules of CSF that may help optimize neutrophil recovery or minimize adverse outcomes have produced mixed results. The results of one study suggest that the presence of monocytopenia can be used to determine the optimal starting time for CSF. Delaying the start of CSF (to day eight) was beneficial in two studies but detrimental (when started at day five) in another study. Priming with CSF was significantly effective in two trials, ineffective in three trials, and produced non-significant benefits in a fourth trial. Administering GM-CSF in the morning versus the evening was associated with a significantly shorter mean duration of grade 3/4 neutropenia in one trial.

- Randomized trials evaluating the use of CSF in the prevention or treatment of mucositis

  In one small study, topical oral G-CSF had a borderline benefit in reducing the incidence of grade 3/4 mucositis, and significantly reduced the duration of hospitalization. In a larger study of G-CSF given by the conventional subcutaneous route, there was significantly less mucositis in the G-CSF arm compared with placebo. In a third study, the duration of established chemotherapy-related mucositis was shorter in patients receiving topical G-CSF compared with povidine-iodine and amphoteracin B. These results are interesting and need to be confirmed in larger randomized studies.

POTENTIAL HARMS

Toxicity of colony-stimulating factor (CSF) is relatively mild. The most consistent clinical symptom attributed to CSF is bone pain reported in incidence rates ranging from 20 to 50%. With the exception of one case, reported bone pain was mild. Other commonly reported adverse effects include injection-site reactions, low-grade fever, headache, and skin rash. Indirect comparisons suggest that more adverse effects were associated with granulocyte macrophage colony-stimulating factor (GM-CSF) than granulocyte colony-stimulating factor (G-CSF).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- It is reasonable to suggest that primary prophylaxis with colony-stimulating factor (CSF) is justified when the anticipated risk of febrile neutropenia is greater than 25 to 40%. However, such risks are rare with the majority of

standard chemotherapy regimens for solid tumours, and evidence comes from cost analysis studies not specific to the Canadian health care system.

CSF reduces the risk of febrile neutropenia associated with standard-dose chemotherapy; however, data are inconclusive as to whether quality of life is significantly improved by its use. Although reduced hospitalization and antibiotic use may be assumed to improve quality of life, dose maintenance with CSF may allow other significant toxicities to emerge (e.g., mucositis, anemia, thrombocytopenia, neuropathies), which can reduce quality of life. The inconvenience of daily injections of CSF and the cost are additional considerations if the risk of neutropenic fever is low.

Since many patients still derive clinical benefit from commonly allowed chemotherapy dose reduction/delay, given the available data, it is not possible to define a cut-off point for acceptable dose reduction/delay before introducing CSF as secondary prophylaxis.

- Many patients with febrile neutropenia have a rapid and uncomplicated recovery on intravenous antibiotics. Although it may be reasonable to reserve CSF use for patients not achieving a rapid improvement (i.e., not defervescing within 48 hours on broad spectrum antibiotics or antibiotic therapy based on the sensitivity of the cultured organism), none of the reported trials assessed the use of CSF delayed in this way. Similarly, as recommended in the guidelines produced by the American Society of Clinical Oncology, it may also be most reasonable to reserve CSF for patients with factors predictive of a poor outcome (e.g., profound neutropenia [absolute neutrophil count <100/microliters], pneumonia, hypotension, multi-organ dysfunction, or invasive fungal infection).

  The efficacy of CSF may be limited in patients with febrile neutropenia or documented sepsis who have received dose-intensive chemotherapy, which is associated with a high risk of febrile neutropenia.

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Campbell C, Bramwell V, Charette M, Oliver T. Role of colony-stimulating factor in patients receiving myelosuppressive chemotherapy for treatment of cancer. Curr Oncol 2003;10(2):102-26.

Systemic Treatment Disease Site Group. Campbell C, Bramwell V, Charette M, Oliver T. The role of colony-stimulating factor (CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Dec [online update]. 33 p. (Practice guideline report; no. 12-2). [76 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Aug 20 (revised online 2003 Dec)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Systemic Treatment Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members past and present, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Systemic Treatment Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of colony-stimulating factor (CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2003 Dec. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995 Feb;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This NGC summary

was updated by ECRI on March 20, 2003. The information was verified by the guideline developer on May 8, 2003. This NGC summary was updated again by ECRI on May 14, 2004. The updated information was verified by the guideline developer on June 2, 2004.

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